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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/787,421	02/26/2004	Majed M. Hamawy	960296.99187	5432

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/28/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/787,421	HAMAWY, MAJED M.	
	Examiner	Art Unit	
	Nora M. Rooney	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/19/2006 and 8/23/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-16 are pending.

2. Applicant's election without traverse of Group I, claims 1-14, is acknowledged.

3. Claims 14-16 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-14 are under examination as they read on a method of monitoring whether an animal is experiencing a disease involving smooth muscle cell abnormalities wherein the disease is transplant rejection.

5. Applicant's IDS documents, filed on 05/19/2004 and 8/23/2004, are acknowledged.

Claim Objections

6. Claims 1 and 6 are objected to because of the following informalities: In claims 1 and 6 the term "proteins having" should be changed to "protein having" because the terms should be in the singular form. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is a resolution step: it is unclear how to determine the kidney transplant rejection status by analyzing the protein of SEQ ID NO:1 or 2. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination.

9. Claim 1 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 6 recite the "degree of presence or absence of a protein." It is unclear how the degree of the presence or absence of the protein correlates with kidney rejection status. Examiner suggests amending the claims to read "presence of a protein" as the term "degree of presence" is indefinite.

Claim 1 recites "is experiencing a disease." It is unclear how one experiences a disease involving smooth muscle cell abnormalities. Examiner suggests amending the claims to recite "has a disease."

Claims 1 and 6 recite "at least one tyrosine" of SEQ ID NO's 1 and 2 have been phosphorylated. Since SEQ ID NO's 1 and 2 each have more than one tyrosine, it is not clear which tyrosine is to be phosphorylated as recited in the claims.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-4, 12-14 and 18-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant is not in possession of a method of monitoring whether an animal is experiencing a disease involving smooth muscle cell abnormalities, the method comprising: analyzing a sample taken from the animal for the degree of presence of a

protein selected from the group consisting of: (a) phosphorylated proteins **having at least 95 percent homology** to phosphorylated SEQ. ID NO. 1 in a form in which at least a tyrosine of SEQ. ID NO. 1 has been phosphorylated; (b) phosphorylated proteins **having at least 95 percent homology** to phosphorylated SEQ. ID NO. 2 in a form in which at least a tyrosine of SEQ. ID NO. 2 has been phosphorylated; (c) proteins **having at least 95 percent homology** to SEQ. ID NO. 1; and (d) proteins **having at least 95 percent homology** to Seq. ID NO. 2, wherein the disease is transplant rejection of claim 1; wherein the animal is a primate of claim 2; wherein the sample is a portion of a specimen selected from the group consisting of the animal's transplanted organ, the animal's transplanted tissue, the animal's kidney, the animal's uterus, the animal's breast, the animal's lung, the animal's heart and the animal's liver of claim 3; wherein the method further comprises examining **protein fragments** solubilized from a homogenate of the sample for the presence of **a fragment of the selected protein which is between 20 kDa and 80 kDa in size** of claim 4; wherein the protein is SEQ. ID NO. 1 in a form in which at least a tyrosine of SEQ. ID NO. 1 has been phosphorylated of claim 5; A method of monitoring whether a transplant selected from the group consisting of transplanted organs, transplanted tissues, and transplanted cells is being rejected by an animal recipient of the transplant, comprising: analyzing a sample taken from the recipient for the degree of presence of a protein selected from the group consisting of: (a) phosphorylated proteins **having at least 95 percent homology** to phosphorylated SEQ. ID NO. 1 in a form in which at least a tyrosine of SEQ. ID NO. 1 has been phosphorylated; (b) phosphorylated proteins **having at least**

95 percent homology to phosphorylated SEQ. ID NO. 2 in a form in which at least a tyrosine of SEQ. ID NO. 2 has been phosphorylated; (c) proteins **having at least 95 percent homology** to SEQ. ID NO. 1; and (d) proteins **having at least 95 percent homology** to SEQ. ID NO. 2 of claim 6; wherein the method comprises examining protein fragments solubilized from a homogenate of the sample for the presence of **a fragment of the selected protein which is between 20 kDa and 80 kDa in size** of claim 7; wherein the animal is a primate of claim 8; wherein the animal is a human of claim 9; wherein the transplant is a transplanted organ selected from the group consisting of transplanted hearts, transplanted livers, transplanted lungs and transplanted kidneys; wherein the sample is a portion of a transplanted organ of claim 11; and wherein the sample is a portion of a transplanted kidney of claim 12; wherein the protein is SEQ. ID NO. 1 in a form in which at least a tyrosine of SEQ. ID NO. 1 has been phosphorylated of claim 13

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (a method of monitoring kidney transplantation status by analyzing a sample for a protein having 95 percent homology to SEQ ID NO:1 or 2) to describe the claimed genus, nor does it provide a description of structural features that are common to species (a method of monitoring kidney transplantation status by analyzing a sample for a protein having 95 percent homology to SEQ ID NO:1 or 2). As discussed above, the

specification provides no structural description of proteins having at least 95 percent homology to SEQ ID NO:1 or 2 other than SEQ ID NO:1 that can be used to monitor transplant rejection status. In essence, the specification simply directs those skilled in the art to go figure out for themselves what **protein** would work. The specification's disclosure is inadequate to describe the claimed genus of a method of monitoring kidney transplantation status by analyzing a sample for a protein having 95 percent homology to SEQ ID NO:1 or 2.

Applicant has disclosed only proteins consisting of SEQ ID NO:1 and 2 for monitoring kidney transplant rejection status; therefore, the skilled artisan cannot envision all the contemplated protein possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the

applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Applicant has disclosed and reduced to practice a single protein species, SEQ ID NO:1 for monitoring kidney transplantation status. The genus of a protein fragment that is "of the selected protein which is between 20 kDa and 80 kDa in size" encompassed by the instant claims has a great deal of variability and includes all as yet undiscovered protein fragments. Applicant has not disclosed, nor does the art recognize, the requisite structural features of the encoded polypeptides which result in the disclosed functional activities of being able to be used to monitor kidney transplantation status, a feature deemed essential to the instant invention. Therefore, one of skill in the art would not recognize Applicant to be in possession of the genus of all protein fragments of proteins that are between 20kDa and 80 kDa in size encompassed by the instant claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: a method of monitoring whether an animal, including a primate, has kidney transplant rejection comprising analyzing a kidney sample taken from the animal for the presence of the phosphorylated protein of SEQ ID NO;1, does not reasonably provide enablement for: a method of monitoring whether an animal is experiencing **a disease involving smooth muscle cell abnormalities**, the method comprising: analyzing **a sample taken from the animal** for the degree of presence of a protein selected from the group consisting of: (a) phosphorylated proteins **having at least 95 percent homology** to phosphorylated SEQ. ID NO. 1 in a form in which at least a tyrosine of SEQ. ID NO. 1 has been phosphorylated; (b) phosphorylated proteins **having at least 95 percent homology** to phosphorylated SEQ. ID NO. 2 in a form in which at least a tyrosine of SEQ. ID NO. 2 has been phosphorylated; (c) **proteins having at least 95 percent homology** to SEQ. ID NO. 1; and (d) **proteins having at least 95 percent homology** to Seq. ID NO. 2, wherein the disease is **transplant rejection** of claim 1; wherein the animal is a primate of claim 2; wherein the sample is **a portion of a specimen selected from the group consisting of the animal's transplanted organ, the animal's transplanted tissue, the animal's**

kidney, the animal's uterus, the animal's breast, the animal's lung, the animal's heart and the animal's liver of claim 3; wherein the method further comprises examining protein fragments solubilized from a homogenate of the sample for the presence of **a fragment of the selected protein which is between 20 kDa and 80 kDa in size** or claim 4; wherein the protein is SEQ. ID NO. 1 in a form in which at least a tyrosine of SEQ. ID NO. 1 has been phosphorylated of claim 5; A method of monitoring whether a transplant selected from the group consisting of **transplanted organs, transplanted tissues, and transplanted cells** is being rejected by an animal recipient of the transplant, comprising: analyzing **a sample** taken from the recipient for the degree of presence of a protein selected from the group consisting of: (a) phosphorylated proteins **having at least 95 percent homology** to phosphorylated SEQ. ID NO. 1 in a form in which at least a tyrosine of SEQ. ID NO. 1 has been phosphorylated; (b) phosphorylated proteins **having at least 95 percent homology** to phosphorylated SEQ. ID NO. 2 in a form in which at least a tyrosine of SEQ. ID NO. 2 has been phosphorylated; (c) proteins **having at least 95 percent homology** to SEQ. ID NO. 1; and (d) proteins **having at least 95 percent homology** to SEQ. ID NO. 2 of claim 6; wherein the method comprises examining protein fragments solubilized from a homogenate of the sample for the presence of **a fragment of the selected protein which is between 20 kDa and 80 kDa in size** of claim 7; wherein the animal is a primate of claim 8; wherein the animal is a human of claim 9; wherein the transplant is a **transplanted organ selected from the group consisting of transplanted hearts, transplanted livers, transplanted lungs and transplanted kidneys**; wherein the

sample is **a portion of a transplanted organ** of claim 11; and wherein the sample is a portion of a transplanted kidney of claim 12; wherein the protein is SEQ. ID NO. 1 in a form in which at least a tyrosine of SEQ. ID NO. 1 has been phosphorylated of claim 13. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

On pages 7-20 of the specification a method is disclosed for analyzing kidney tissue samples for the phosphorylated protein of SEQ ID NO:1 to determine kidney transplant rejection status. Experiments were performed by immunoblot using of anti-phosphotyrosine antibody after SDS-PAGE 2 D gel electrophoresis, polyacrylamide electrophoresis, mass spectrometry, immunohistochemistry, light microscopy and RT-PCR from kidney tissue samples of mice, rhesus monkeys, baboons and rats.

The specification fails to provide sufficient enablement for a person of skill in the art to make and use any phosphorylated proteins **having at least 95 percent homology** to: phosphorylated SEQ. ID NO. 1 in a form in which at least a tyrosine of SEQ. ID NO. 1 has been phosphorylated, phosphorylated proteins **having at least 95 percent homology** to phosphorylated SEQ. ID NO. 2 in a form in which at least a tyrosine of SEQ. ID NO. 2 has been phosphorylated, proteins **having at least 95 percent homology** to SEQ. ID NO. 1, or proteins **having at least 95 percent homology** to Seq. ID NO. 2 to determine kidney transplant rejection status in an animal. The specification and claims offer no guidance as to what particular proteins, other than the peptide of SEQ ID NO:1, that are required to monitor disease. A myriad of proteins are encompassed by the claims. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly may encompass a significant number of inoperative species. The claims encompass any protein with a specified homology to SEQ ID NO:1 or SEQ ID NO:2. There is great unpredictability in the art and an undue amount of experimentation is required to practice the claimed invention.

Claims 4 and 7 make reference to examining protein fragments for the presence of a fragment of the homogenate of the sample which is between 20 kDa and 80kDa in size to monitor kidney transplant rejection status. These terms recite no structure for

the protein fragment. There is a lack of direction and guidance as to which fragments would effectively monitor kidney transplantation status in the claimed invention. There is also a lack of guidance given as to the significance of amino acid differences at given positions within the protein, though the importance of homology at certain positions is well known the art. The claims encompass many proteins that would not work. Therefore, an undue amount of experimentation is required to enable one of skill in the art to practice the claimed invention.

The art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases and recognized that it was unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences. Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

The specification does not provide sufficient support for the a sample that is a portion of a specimen of an animal's transplanted organ, an animal's transplanted tissue, an animal's uterus, an animals' breast, an animal's lung, an animal's heart or an animal's liver as recited in claim 3. The specification only provides support for a tissue sample form an animal's kidney.

The specification does not provide support for a transplant selected from transplanted organs, transplanted tissues, and transplanted cells as recited in claim 6. The specification only provides support for a tissue sample from an animal's kidney transplant.

The specification does not provide sufficient support for a transplanted heart, a transplanted liver or a transplanted lung as recited in claim 10. The specification only provides support for a transplanted kidney.

The specification does not provide support for "a sample" in claims 1 and 6. The specification only provides support for a transplanted kidney tissue sample.

The specification does not provide support for monitoring disease with un-phosphorylated proteins of SEQ ID NO:1 and 2 as recited in parts c and d of claim 1 or with the fragments of claims 4 and 7. It is unclear as to whether the presence of the un-phosphorylated protein of SEQ ID NO:1 or 2 or fragments thereof correlates with

transplant rejection status because the protein of SEQ ID NO:1 and 2 is present in normal and diseased tissue.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina

Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 19, 2006

Nora M. Rooney, M.S., J.D.

Patent Examiner

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12/20/06